IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **LEE, Kyu Hyun**	)	Group Art Unit: **1633**
Serial No.: **10/584,383**	)	Examiner: **HIRIYANNA, K.T.**
Filed: **06/26/2006**	)	Confirmation No.: **3667**
For: **THERAPEUTIC AGENT FOR TREATMENT OF CANCER COMPRISING HUMAN APOLIPOPROTEIN (A) KRINGLES LK68 OR LK8 GENES AS EFFECTIVE INGREDIENT, AND METHOD FOR TREATING CANCER USING THE SAME**	)	

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REASONS IN SUPPORT OF PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

The reasons provided herein are in support of the Pre-Appeal Brief Request for Review (form PTO/SB/33) submitted herewith, which is in reply to the "final" Office Action mailed May 28, 2008, which set August 28, 2008 as the initial deadline for response. This submission is believed to be timely filed.

A Notice of Appeal and the necessary fee of $255.00 are submitted herewith.

Reconsideration in light of the following reasons is respectfully requested.

Alleged Rejection under 35 U.S.C. § 103(a)

Claims 1-23 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over a combination of Chang et al. (WO 01/19868 A1) and Trieu et al. (1999, BBRC 257:714-718). Applicants have carefully reviewed the statement of rejection as well as the cited documents

and respectfully traverse because no *prima facie* case of obviousness is present. Reconsideration in light of the following is respectfully requested.

The standards for a *prima facie* case of obviousness after the Supreme Court's binding decision in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) continue to include the absolute requirements for 1) clear articulation of the rationale for asserting obviousness and 2) a reasonable expectation of success in achieving the subject matter asserted as obvious (see MPEP 2141 and 2144, for example). With respect to requirement 1), the rationale may be in the form of clearly articulated reasons for the modification of cited documents to arrive at the claimed subject matter (see MPEP 2141 III(G)). But regardless of whether there is an adequate rationale, there remains requirement 2) and the need for a reasonable expectation of success in modifying the cited documents to arrive at the claimed subject matter.

Additionally, the concept of a *prima facie* case is that a preponderance of the evidence supports the rejection (see MPEP 2142, for example). This legal standard as set forth by MPEP 2142 and the case decisions cited therein "requires the evidence [supporting the rejection] ***to be more convincing*** than the evidence which is offered in opposition to it." This legal standard applies equally to both of the requirements stated above. Moreover, this standard is applied to *the entire record with due consideration to the persuasiveness of any arguments and any secondary evidence*. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992).

Applicants respectfully submit that as provided below, there is insufficient evidence of a reasonable expectation of success to support a *prima facie* case of obviousness.

Basis of the Instant Rejection and Lack of a Reasonable Expectation of Success

The instant rejection appears to be summarized on page 4, second full paragraph, of the Action mailed May 28, 2008, which is reproduced below.

> Thus it would have been obvious to one of skill in the art to substitute the full length apo(a) fragment in the gene therapeutic vector construct of Trieu or a viral vector described in prior art with a fragment of apo(a) gene that codes for LK68 and LK8 kringles and prepare a composition and treat a solid tumor or metastasis of thereof in an animal subject. One of the skill in the art would have been motivated to use the gene fragment that codes for LK68 and LK8 kringles in specific viral vector/or vector transfected as these gene carriers increase the efficacy of a tumor gene therapy. One of skill in the art would have an expectation of success of making and using a pharmaceutical composition for gene therapy of tumors using gene coding sequences for kringles KIV9-KIV10-KV (LK68) or KV (LK8) cloned in viral or non-viral vectors as the art at the time of invention teaches that sub-cloning of gene fragments in therapeutic vectors and their therapeutic use is routine. Further it would have been obvious to try using different vectors described in the art of tumor gene therapy to deliver and express LK68 and LK8 kringles. Thus the invention as claimed would have been *prima facie* obvious to one of skill in the art.

As indicated by the above quote, the instant rejection is based upon the contention that it would have been obvious to one of skill in the art to place sequences encoding LK68 and LK8, as reported by Chang et al., into the vector constructs of Trieu et al. with the expectation of using them as gene carriers to "increase the efficacy of a tumor gene therapy." While this may be a summary of the rationale for the modification of the Trieu et al. document based on the Chang et al. document, the alleged expectation of success is that "therapeutic use [of vectors] is routine."

During the telephonic interview of June 26, 2008 between the undersigned and Examiners K.T. Hiriyanna, R. Kelly, and J. Woitach, the Examiners contended that Chang et al. provided additional expectation of success because they report the LK68 and LK8 peptides as having activity when directly administered as protein therapy *which is in contrast to the pending claims, **featuring gene therapy***. Applicants point out that Chang et al. are silent as to use of nucleic acids to express the proteins as a part of gene therapy for therapeutic purposes.

This contention by the Examiners only reflects a part of the entire record. So consideration of the entire record, as required by the Federal Circuit in *In re Oetiker*, cannot ignore, or minimize without cause, other evidence of record.

The evidence of record includes express statements in the Trieu et al. document, reporting tumor suppression in mice via CHO cells expressing a full length, recombinant apo(a) protein with 18 kringle 4 domains while CHO cells expressing a truncated apo(a) protein with only six kringle 4 domains did not exhibit delayed tumor growth nor did it impair angiogenesis. More specifically, Trieu et al. report that Ha6, consisting of 6 repeated kringle 4 domains and one kringle 5 domain failed to suppress tumor angiogenesis (see Figure 1 and page 715 of Trieu et al.). Trieu et al. then continue by stating that "[t]his observation provides unprecedented evidence that a large number of kringle 4 repeats is necessary for the biologic activity of apo(a) as an inhibitor of tumor angiogenesis and growth" (see end of page 715, second to last sentence). The authors further state that "it is of interest that only full length apo(a) localized to tumor microvessels. The fact that truncated apo(a) did not localize to tumor microvessels suggests that the missing kringle 4 domains are necessary for the binding of apo(a) to tumor microvessels to exert its anti-angiogenic effects" (see sentence bridging pages 716-717).

The Trieu et al. document thus clearly argues against a reasonable expectation of success in practicing the claimed subject matter of treating tumors via gene therapy to express a severely truncated human apo(a) peptide (consisting of only two kringle 4 domains, in the case of LK68, or a single Kringle 5 domain, in the case of LK8.

But Applicants respectfully point out that a second document of record is present to indicate a lack of a reasonable expectation of success. Kuo et al. (2001, PNAS 98:4605-4610) report that an adenovirus based vector system used to express endostatin or angiostatin demonstrated little or no inhibition of tumors in an animal model despite potent antitumor effects of endostatin and angiostatin when delivered directly as protein therapy. This report clearly counteracts any expectation of success alleged to be presented by Chang et al. because it is a direct comparison of the two polypeptides (endostatin and angiostatin) when administered via protein therapy or gene therapy. If these two anti-angiogenesis polypeptides did not function when administered via gene therapy, there is no expectation that the LK68 and LK8 polypeptides of Chang et al. would retain function when administered via gene therapy.

And with respect to the Examiners' contention (raised during the telephonic interview) that Kuo et al. provided the artisan of ordinary skilled with the expectation of manipulating the LK68 and LK8 encoding nucleic acids for expression in a mammalian cell, Applicants

respectfully point out that mere ability to recombinantly use different vectors, promoters, or cells is not a substitute for the requirement of an adequate expectation of success when Kuo et al. teach failure in using gene therapy to deliver the two anti-angiogenic polypeptides.

In light of the above, consideration of the entire record includes the evidence by Chang et al., Trieu et al., and Kuo et al. where **two of these three** documents teach away from an expectation of success in making and using the claimed invention. Applicants thus respectfully submit that there is **no** preponderance of evidence supporting the requirement for a reasonable expectation of success. Without a preponderance of the evidence, no *prima facie* case of obviousness is possible.

Instead, the only expectation of success is found in the instant application, where there is demonstration of successful use of nucleic acids to express LK68 and LK8 in the therapeutic methods of claims 18-21 (such as described in Examples 3-11). With such success, no more than routine and repetitive experimentation is needed to practice the claimed methods.

Conclusion

In light of the foregoing, Applicants submit that the sole remaining issue in this case, that of a single rejection alleging obviousness, is misplaced and may be properly withdrawn. Because the rejection is misplaced, it is believed that the application is in condition for allowance. Applicants urge the issuance of a notice of Allowance in due course. The Office is encouraged to contact the undersigned to further the prosecution of the present invention.

Respectfully submitted,

JHK Law

Dated: July 24, 2008

By: /Joseph Hyosuk Kim/

Joseph Hyosuk Kim, Ph.D.

Reg. No. 41,425

P.O. Box 1078
La Canada, CA 91012-1078
(818) 249-8177 - direct
(818) 249-8277 - fax